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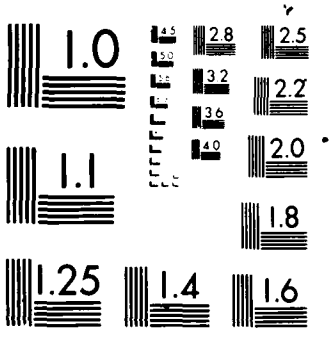

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CHEMOTHERAPY OF RODENT MALARIA

Final Report

by

WALLACE PETERS MD DSc

1 October 1981 - 30 September 1982

Supported by

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Fort Detrick, Frederick, Maryland 21701

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Department of Medical Protozoology

London School of Hygiene and Tropical Medicine

Keppel Street

London, WCIE 7HT, UK

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1. INTRODUCTION

This is the second full Annual Report to be submitted by the Principal Investigator since the commencement of WRAIR sponsored malaria chemotherapy research at the London School of Hygiene and Tropical Medicine. The programme is now gathering momentum and our routine techniques are well established. During the following twelve months we expect to have introduced a number of additional lines of approach to maximise the potential of this programme.

2. ADMINISTRATIVE EVENTS

Staff employed on US Army funds are as follows:

Senior Technologist - Mr B L Robinson	50% time
Junior Technician - Ms A West	100% time

Other staff associated with this project but paid from School sources are as follows:

Professor W Peters (PI)	20% time
Dr D C Warhurst (Biologist)	20% time
Dr D S Ellis (Electron Microscopist)	10% time
Dr W E Ormerod (Biologist-Pharmacologist)	20% time

The new laboratory and insectary unit at Winches Farm Field Station is now completed and functioning. We have an established colony of Anopheles stephensi (Beech strain) running and Plasmodium yoelii nigeriensis is being routinely passaged through the mosquitoes. A full range of resistant strains of rodent malaria is being maintained either by animal passage or in the cryobank.

A total of five new compounds have been received from WRAIR during the period covered by this contract.

3. CHEMOTHERAPY STUDIES

3.1 Causal prophylaxis

Causal prophylactic tests have been performed on nineteen WRAIR compounds and detailed summary sheets are attached in the Appendix (Tables 1 through 21). All but three of these compounds are 8-aminoquinolines.

The structure-activity relationships of this interesting series of primaquine analogues reveals some interesting features. The 2-CH_3 and 3-CH_3 derivatives increase the activity whereas the addition of a CH_3 at the 4 position by itself makes little difference. Whereas the 5-OCH_3 analogue was inactive at the MTD, the 5-OCH_3, 2-CH_3 analogue was rather more active than primaquine.

The 5-mCH_3 phenoxy analogue (WR 215295) was inactive at the MTD but the addition of a 3-CH_3 or the 2-OCH_3, 4-CH_3 derivative were more active than primaquine.

The most interesting series were the 5-alkyloxy analogues, the activity depending on the length of the sidechain. Of those tested to date, the 7 carbon compound, WR 246315 was the most active, with a MFED of 1-3 mg/kg. The 6 carbon compound WR 228708 was less active than primaquine but its 4-CH_3 analogue WR 242511 was very active. The 4-carbon compound WR 228000 was more active than primaquine (MFED 10-30 mg/kg), and equal to the 12 carbon, 4-CH_3 analogue WR 243789.

The 4-CH_3, 6-CH_3S analogue of primaquine was inactive at the MTD.

Of the remaining compounds WR 61112 (clopidol) was inactive at 30 mg/kg, WR 158124 active at 10-30 mg/kg and the guanylhydrazone WR 9792 active at 3-10 mg/kg, the latter two compounds without evidence of residual activity on blood stages.

Still awaiting test are the primaquine analogues WR 228583 with a 4 carbon at the 5 - O position, WR 247705, the 5 carbon, 4-CH_3 analogue and WR 248412, the 8 carbon analogue. We also have still in test a number of putative primaquine metabolites from WRAIR and WHO which will be reported upon in our next report.

3.2 Blood schizontocides

In addition to the normal "four day tests" carried out on WRAIR compounds, the details of which are appended as Tables 22 through 32, we have also been examining some compounds to determine the ED_{50} and ED_{90} when administered as a single dose. These studies are in connection with our work on resistance to mefloquine and summary sheets are included in the Appendix (Tables 33 through 48).

The activity of two compounds WR 245082 and 246976 were compared directly with floxacrine. Neither were as effective in the N strain. All were effective in the NS line and the mefloquine resistant N/1100 line. The clopidol analogue WR 159251 which was active against the N strain only at a high dose level and with a very flat dose-activity curve, proved to be active against the NS and N/1100 lines. This compound will be compared with clopidol itself (WR 61112) in the 4-day test.

3.3 Drug combinations

A study to determine the nature of the interaction of mefloquine with a mixture of pyrimethamine and sulfadoxine (1:3) was carried out by calculating the ED_{90} of each compound alone and of a range of combined doses (Tables 49 through 54). These values were used to plot a graph to demonstrate the presence of potentiation,

antagonism or a simple additive effect (Figure 1). If potentiation were present the curve of the graph would be below the line joining the ED_{90} values of the pyrimethamine-sulfadoxine mixture and mefloquine when given independently of each other. It is apparent, however, that the ED_{90s} of the triple combination fall along that line indicating that only an additive effect is present.

3.4 Development and prevention of drug resistance

In our Annual Report for 1980 - 1981 (Contract DAMD-17-G-9473) we described our preliminary studies on the effects of administering a mixture of mefloquine with a pyrimethamine-sulfadoxine (PS) combination using the relapse technique ie fixed single drug dose at the time of infection. We have now carried out further work on this and have extended the study to include a line which has been developed from a PS resistant parent strain.

The three lines which we have established are:-

PFM - derived from the drug sensitive P.berghei N (= Keyberg 173)

MPS - derived from the moderately chloroquine-resistant "P.berghei NS", actually a subspecies of P.yoelii (Peters et al. 1978)

MFY - derived from P.berghei FY (= NK65 PS of Peters, 1974). The latter was developed originally as a PS resistant line and was subsequently found to be highly resistant to a 1:3 PS mixture eg 320 mg/kg at the time of passage was almost totally ineffective.

For comparison, data have been plotted against those from two other mefloquine-resistant lines, the N/1100 derived from P.berghei N and the NS/1100 derived from "P.berghei NS", produced by the same technique. In plotting the data we have adopted in the ordinate the ratio between the "2% delay time" of the infection in later passages to that observed in the first passage to indicate the manner in which this decreased over time. Since the numbers of days between individual passages varied during the course of the experiments depending on the level of adaptation of the parasites, we have plotted on the abscissa the number of days since the lines were started rather than the passage number. These graphs are shown in Figure 2.

Figure 2a illustrates a marked difference in the rate at which the drug P.berghei N parasites became resistant to mefloquine alone and to the MPS mixture. It required over 200 days before the PFM line showed a similar delay pattern to that developed by the N/1100 in a mere 40 days. Note also that the N/1100 line did not become completely unresponsive to M during the 80 days over which it was observed.

In contrast the NS/1100 line was started from "P.berghei NS" which has an inher nt low-level resistance to chloroquine. This line rapidly became totally unresponsive to M. The opposite was observed with the MPS line (Figure 2b) which maintained a high level of sensitivity for the first 100 days, and only a moderate reduction in response over the next 100 days.

The MFY line, originally resistant to PS showed a rapid decrease of its response to the triple mixture but, surprisingly, the response seemed to stabilise after 30 or 40 days at a moderate level of resistance only.

Further experiments are needed to determine how stable the resistance of these lines would be in the absence of drug selection pressure and these are scheduled to commence shortly. It is also necessary to observe the effect of passaging the MPS line cyclically through A.stephensi.

3.5 Mode of drug action

As part of our programme to investigate the mode of action of WR225448 ultrastructural studies on animals which had been treated were carried out. Since in some of our initial studies the livers of treated animals showed some effects which were, possibly, unconnected with the infection, we examined samples from treated but uninfected controls. We found that liver damage had occurred and that the liver cells were vacuolated and disrupted. There were considerable lipid deposits and many of the mitochondria were affected. In general the liver had a fairly toxic appearance (Figure 3).

Infected liver sections from animals treated with a single dose of 1 mg/kg of WR 225448 show normal peripheral enzyme production, but no liberation of enzyme granules. Adjacent hepatocyte tissue is apparently unaffected at the interface between the schizont and hepatocyte (Figure 4).

When examined at a higher magnification the extensive enzyme granule production and swollen mitochondria are clearly seen. In addition many of the nuclei in the schizonts show marked separation and blebbing of their surrounding membranes are apparent (Figure 5). A paper on this work is in preparation.

4. PAPERS PUBLISHED

4.1 Already published

Landau, I., Boulard, Y., Seureau, C. and Peters, W. (1982) Schizogonie hepatique retardee par l'ethionie ou carences en methionine: etude histologique et ultrastructurale. Ann.Parasitol. (Paris) 57, 1-20.

Peters, W. 4- and 8-aminoquinolines, chinin und chiniahnliche verbindungen. In: "Malaria: Diagnose, Klinik, Therapie", (Leichert, K.H.Ed.), Roche, Grenzach-Wyhlen, pp. 149-168.

Peters, W. Suggestions for field research relating to drug-resistant P.falciparum. Joint FIELDMAL/CHEMAL SWG and SEAR/WPR principal investigators meeting on drug-resistant malaria, Kuala Lumpur, 10-15 August 1981.

Peters, W. Policies on drug use aiming at preventing, delaying or reversing the selection of resistant P.falciparum parasites. Joint FIELDMAL/CHEMAL SWG and SEAR/WPR principal investigators meeting on drug-resistant malaria, Kuala Lumpur, 10-15 August 1981.

Peters, W. Problems with presently used antimalarial drugs. Working paper for WHO 5th CHEMAL SWG, Washington, May/June 1982.

Peters, W. Future deployment of mefloquine and essential measures for protecting mefloquine against resistance. In: Drug-resistant malaria. The report of a meeting held in Kuala Lumpur, Malaysia, 10-15 August 1981. (Ed. W.Wernsdorfer) Geneva UNDP/ World Bank/WHO Special Programme for Research and Training in Tropical Diseases, pp 123-128.

Peters, W. (1982). Antimalarial drug resistance - an increasing problem. Brit.Med.Bull., 38, 187-192.

Peters, W., James, D.M., Li Ze-Lin and Robinson, B.L. (1981). Antimalarial activity of Arteannuin (Artemisinine, Quinghaosu), a Chinese plant derivative against Plasmodium berghei: preliminary data. Trans.R.Soc.Trop.Med.Hyg., 75, 4.

Peters, W. and Robinson, B.L. (1982). Value of a triple combination in delaying the development of drug resistance in a rodent malaria. Paper presented at ICOPA V, held in Toronto, Canada, 7-14 August 1982.

4.2 In press

Boulard, Y., Ellis, D., Landau, I., Miltgen, F. and Peters, W. (1983) The chemotherapy of rodent malaria XXXIV. Causal prophylaxis. Part III: Ultrastructural changes induced in exoerythrocytic schizonts of Plasmodium yoelii by primaquine. Ann.Trop.Med.Parasitol.

Gu, H.M., Warhurst, D.C. and Peters, W. Rapid action of Quinghaosu and related drugs on incorporation of 3H isoleucine by Plasmodium falciparum in vitro. Submitted to Biochem.Pharmacol.

Knight, D.J., Mamalis, P. and Peters, W. (1983). The antimalarial activity of N-benzyl oxyhydrotriazines, Part III: the activity of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(2,4,5-trichloropropyloxy)-1,3,5-triazine hydrobromide (BRL51084) and hydrochloride (BRL5231). Ann.Trop.Med.Parasitol.

Li, Z.L., Gu,H.M., Warhurst, D.C. and Peters, W. (1982). Effects of Quinghaosu and related compounds on incorporation of G-3H hypoxanthine by Plasmodium falciparum in vitro. Trans.R.Soc.Trop. Med.Hyg.

Peters, W. The interaction of drugs and immunity in malaria. (Arun Banerjee Oration, Calcutta, 1980). Proceedings of the Symposium on a Hundred Years of Malaria Research.

Peters, W. The menace of multiple-drug-resistant malaria. Paper presented at the 7th Saudi Medical Meeting, Dammam, May 1982.

Peters, W. and Richards, W.H.G. (Eds.) Handbook of Pharmacology - Antimalarials. Chapters 16, 18, 24 and 34.

Peters, W. and Robinson, B.L. (1983). The chemotherapy of rodent malaria XXXV. Further studies on the retardation of drug resistance by the use of a triple combination of mefloquine, pyrimethamine and sulfadoxine in mice infected with P.berghei and "P.berghei NS". Ann.Trop.Med.Parasitol.

Peters, W. New Answers Through Chemotherapy? In: The Present State of Malaria Research Worldwide. Experientia.

5. APPENDICES

5.1 Summary of causal prophylactic test data (Table 1)

5.2 Individual causal prophylactic test reports (Tables 2-21)

5.3 Summary of blood schizontocidal (4 day test) data (Table 22)

5.4 Individual blood schizontocidal (4 day test) reports (Tables 23-32)

5.5 Summary of blood schizontocidal (single dose) data (Table 33)

5.6 Individual blood schizontocidal (single dose) reports (Tables 34-48)

5.7 Interaction of mefloquine with pyrimethamine/sulfadoxine (1:3 mixture) in P.berghei (Figure 1).

5.8 Changing trends of 2% delay times for lines developed from P.berghei N, NS and FY strains (Figure 2)

5.9 Electron micrographs showing effects of WR 225,448 against EE stages of P.yoelii (Figures 3,4,5).

TABLE 1

SUMMARY OF CAUSAL PROPHYLACTIC TESTS

LON	BN	WR	MFED mg/kgx1	RESIDUAL ACTIVITY at D+2	COMMENT
1711	BJ08241	2975	30 - 60	NIL AT 60	Primaquine diphosphate
1715	AG99266	5990	NA at MTD	NIL AT MTD(=10.0)	8-aminoquinoline
1719	BE50003	181023	>30	NIL AT 30	8-aminoquinoline 4-methylprimaquine
1720	BE17580	182234	3.0 -10.0	NIL AT 30	8-aminoquinoline
1721	ZP12775	211814	3.0 -10.0	NIL AT 30	8-aminoquinoline
1722	ZN43444	215295	NA at 30	NIL AT 30	8-aminoquinoline
1723	ZN81499	228000	10 - 30	NIL AT 30	8-aminoquinoline
1725	BH13989	233627	10 - 30	NIL AT 30	8-aminoquinoline
1726	BH35770	235485	10 - 30	NIL AT 30	8-aminoquinoline
1727	BH69990	238605	10 - 30	PRESENT AT 30	8-aminoquinoline
1728	BJ08189	243789	10 - 30	NIL AT 30	8-aminoquinoline
1729	BJ45691	246315	1.0-3.0	NIL AT 3.0 PRESENT AT 30	8-aminoqinoline
1732	BH58120	237375	NA at 100	NIL AT 100	8-aminoquinoline
1733	BG66798	228708	30 -100	NIL AT 100	8-aminoquinoline
1734	BH89438	242511	3.0	NIL AT 30	8-aminoquinoline
1736	BJ78592	242511	3.0	NIL AT 100	8-aminoquinoline
1716	AJ63248	9792	3.0-10.0	NIL AT 30	guanylhydrazone
1717	AB65541	61112	NA at 30	NIL AT 30	clopidol
1718	BD22997	158124	10 - 30	NIL AT 30	miscellaneous

PRINCIPAL INVESTIGATOR: PROFESSOR W.PETERS
DEPARTMENT OF MEDICAL PROTOZOOLOGY
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

DATE: 14th January'8

CAUSAL PROPHYLAXIS TEST NO: 964 DATE: 8/7/82

COMPOUND: LON/ 1711 BOTTLE NO: BJ08241 WR2975

FORMULATION: Tween 80/H_2O ROUTE: sc/~~ip/po~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
	5/5	3/3	(a) 5.12	(c) 3.27				
	5/5	3/3	(b) 5.27	(d) 3.46	NIL	NIL	NIL	INACTIVE
	5/5	3/3	(b) 5.67	(d) 3.42	NIL	NIL	NIL	INACTIVE
	3/5	3/3	(b) > 8.77	(d) 3.37	> 3.65	NIL	> 3.65	ACTIVE
	0/5	3/3	(b) > 14	(d) 3.29	> 8.88	NIL	> 8.88	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ...30.-.60.....mg/kg

RESIDUAL ACTIVITY: NIL

~~XXXXXXX~~ AT ..60.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1148 DATE: 28/9/82

COMPOUND: LON/ 1715 BOTTLE NO: AG99266 WR5990

FORMULATION: Tween 80/H_2O ROUTE: sc/~~ip/po~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.61	(c) 3.14				
3.0	3/3	3/3	(b) 5.45	(d) 3.21	NIL	NIL	NIL	INACTIVE
10.0	3/3	3/3	(b) 5.82	(d) 3.16	NIL	NIL	NIL	INACTIVE
30.0	0/3	0/3	(b) -	(d) -	-	-	-	> LD_{100}
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ...> MTD.....mg/kg

RESIDUAL ACTIVITY: NIL

~~PRESENT~~ AT ..MTD.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1148 DATE: 28/9/82

COMPOUND: LON/ 1719 BOTTLE NO: BE50003 WR181023

FORMULATION: Tween 80/H_2O ROUTE: sc/~~XXXX~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.61	(c) 3.14				
3.0	3/3	3/3	(b) 5.64	(d) 3.17	NIL	NIL	NIL	INACTIVE
10.0	3/3	3/3	(b) 5.78	(d) 3.15	NIL	NIL	NIL	INACTIVE
30.0	2/3	3/3	(b) > 10.83	(d) 3.24	> 5.22	NIL	> 5.22	ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ...>30.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~MARKED~~ AT .....30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1148 DATE: 28/9/82

COMPOUND: LON/ 1720 BOTTLE NO: BE17580 WR182234

FORMULATION: Tween 80/H_2O ROUTE: sc/~~XXXX~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
			(a)	(c)				
Ø	5/5	3/3	5.61	3.14				
			(b)	(d)				
3.0	2/3	3/3	>10.82	3.22	> 5.21	NIL	> 5.21	ACTIVE
			(b)	(d)				
10.0	0/3	3/3	> 14	3.20	> 8.59	NIL	> 8.59	FULLY ACTIVE
			(b)	(d)				
30.0	0/3	3/3	> 14	3.24	> 8.59	NIL	> 8.59	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ....3.0.-.10.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~XXXXXX~~ AT ....10.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1148 DATE: 28/9/82

COMPOUND: LON/ 1721 BOTTLE NO: ZP12775 WR211814

FORMULATION: Tween 80/H_2O ROUTE: sc/~~XXXX~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.61	(c) 3.14				
3.0	3/3	3/3	(b) 5.58	(d) 3.16	NIL	NIL	NIL	INACTIVE
10.0	0/3	3/3	(b) > 14	(d) 3.17	> 8.59	NIL	> 8.59	FULLY ACTIVE
30.0	0/3	3/3	(b) > 14	(d) 3.23	> 8.59	NIL	> 8.59	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ...3.0.-.10.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~XXXXXXX~~ AT ...30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1055 DATE: 24/8/82

COMPOUND: LON/ 1722 BOTTLE NO: ZN43444 WR215295

FORMULATION: Tween 80/H_2O ROUTE: sc/XXXXX TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.21	(c) 3.32				
3.0	3/3	3/3	(b) 5.15	(d) 3.28	NIL	NIL	NIL	INACTIVE
10.0	3/3	3/3	(b) 5.38	(d) 3.30	NIL	NIL	NIL	INACTIVE
30.0	3/3	3/3	(b) 5.81	(d) 3.34	NIL	NIL	NIL	INACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE .....>30.0.....mg/kg

RESIDUAL ACTIVITY: NIL

XXXXXX AT .30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1055 DATE: 24/8/82

COMPOUND: LON/ 1723 BOTTLE NO: ZN81499 WR228000

FORMULATION: Tween 80/H_2O ROUTE: sc/~~XXXXX~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.21	(c) 3.32				
3.0	3/3	3/3	(b) 5.48	(d) 3.18	NIL	NIL	NIL	INACTIVE
10.0	3/3	3/3	(b) 8.95	(d) 3.26	3.74	NIL	3.74	ACTIVE
30.0	0/3	3/3	(b) > 14	(d) 3.28	> 8.79	NIL	> 8.79	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE .....10.0 - 30.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~XXXXXX~~ AT ...30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 1055 DATE: 24/8/82

COMPOUND: LON/ 1725 BOTTLE NO: BH13989 WR233627

FORMULATION: Tween 80/H_2O ROUTE: sc/~~XXXX~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.21	(c) 3.32				
3.0	3/3	3/3	(b) 5.34	(d) 3.37	NIL	NIL	NIL	INACTIVE
10.0	2/3	3/3	(b) > 8.65	(d) 3.34	> 3.44	NIL	> 3.44	ACTIVE
30.0	0/3		(b) > 14	(d) 3.37	> 8.79	NIL	> 8.79	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ...10.0.-.30.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~XXXXXXX~~ AT ....30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1282 DATE: 12/11/82

COMPOUND: LON/1726 BOTTLE NO: BH35770 WR235485

FORMULATION: Tween 80/H_2O ROUTE: sc/~~XXXX~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	4/4	3/3	(a) 5.87	(c) 3.82				
3.0	2/3	3/3	(b) > 8.59	(d) 3.76	> 2.72	NIL	> 2.72	SLIGHTLY ACTIVE
10.0	1/3	3/3	(b) >12.10	(d) 3.83	> 6.23	NIL	> 6.23	ACTIVE
30.0	0/3	3/3	(b) > 14	(d) 3.79	> 8.13	NIL	> 8.13	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE 10.0 - 30.0 .....mg/kg

RESIDUAL ACTIVITY: NIL

~~XXXXXX~~ AT 30.0 .....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1282

DATE: 12/11/82

COMPOUND: LON/ 1727

BOTTLE NO: BH69990 WR238605

FORMULATION: Tween 80/H_2O

ROUTE: sc/~~ip/po~~

TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice

PARASITE: P. yoelii nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	4/4	3/3	(a) 5.87	(c) 3.82				
3.0	3/3	3/3	(b) 6.99	(d) 3.86	1.12	NIL	1.12	SLIGHTLY ACTIVE
10.0	2/3	3/3	(b) > 9.14	(d) 4.01	> 3.27	NIL	> 3.27	ACTIVE
30.0	0/3	3/3	(b) > 14	(d) 7.23	> 8.13	3.41	> 4.72	FULLY ACTIVE, SOME RESIDUAL ACTIVITY.
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ...10.0 - 30.0.....mg/kg

RESIDUAL ACTIVITY: ~~XXX~~

PRESENT AT ....30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 1282 DATE: 12/11/82

COMPOUND: LON/ 1728 BOTTLE NO: BJ08189 WR243789

FORMULATION: Tween 80/H_2O ROUTE: sc/~~xxxx~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

Dose mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	4/4	3/3	(a) 5.87	(c) 3.82				
3.0	2/3	3/3	(b) > 8.82	(d) 3.68	> 2.95	NIL	> 2.95	SLIGHTLY ACTIVE
10.0	1/3	3/3	(b) >12.12	(d) 3.79	> 6.25	NIL	> 6.25	ACTIVE
30.0	0/3	3/3	(b) > 14	(d) 3.84	> 8.13	NIL	> 8.13	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE 10.0 - 30.0 .....mg/kg

RESIDUAL ACTIVITY: NIL

~~XXXXXXX~~ AT ....30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1282 DATE: 12/11/82

COMPOUND: LON/ 1729 BOTTLE NO: BJ45691 WR246315

FORMULATION: Tween 80/H_2O ROUTE: sc/~~ip/po~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	4/4	3/3	(a) 5.87	(c) 3.82				
3.0	0/3	3/3	(b) > 14	(d) 3.95	> 8.13	NIL	> 8.13	FULLY ACTIVE
10.0	0/3	3/3	(b) > 14	(d) 4.26	> 8.13	NIL	> 8.13	FULLY ACTIVE
30.0	0/3	3/3	(b) > 14	(d) 6.78	> 8.13	2.96	> 5.17	FULLY ACTIVE, SOME RESIDUAL ACTIVITY.
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE .....< 3.0.....mg/kg

RESIDUAL ACTIVITY: ~~XXX~~

PRESENT AT .30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 1377

DATE: 7/12/82

COMPOUND: LON/ 1729

BOTTLE NO: BJ45691 WR246315

FORMULATION: Tween 80/H_2O

ROUTE: sc/~~ip/po~~ XXXXX

TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice

PARASITE: P. yoelii nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.44	(c) 3.47				
0.3	3/3	3/3	(b) 4.99	(d) 3.43	NIL	NIL	NIL	INACTIVE
1.0	2/3	3/3	(b) > 8.18	(d) 3.48	> 2.74	NIL	> 2.74	SLIGHTLY ACTIVE
3.0	0/3	3/3	(b) > 14	(d) 3.56	> 8.56	NIL	> 8.56	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE .....1.0 - 3.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~PRESENT~~ XXXXXXX AT ...3.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 1377 DATE: 7/12/82

COMPOUND: LON/ 1732 BOTTLE NO: BH58120 WR237375

FORMULATION: Tween 80/H_2O ROUTE: sc/[illegible] TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0	5/5	3/3	(a) 5.44	(c) 3.47				
3.0	3/3	3/3	(b) 4.87	(d) 3.46	NIL	NIL	NIL	INACTIVE
10.0	3/3	3/3	(b) 5.10	(d) 3.53	NIL	NIL	NIL	INACTIVE
30.0	3/3	3/3	(b) 4.81	(d) 3.47	NIL	NIL	NIL	INACTIVE
100.0	3/3	3/3	(b) 4.61	(d) 3.52	NIL	NIL	NIL	INACTIVE
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ....>.100.0.....mg/kg

RESIDUAL ACTIVITY: NIL

[illegible] AT .100.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR [illegible]
Department of Medical Protozoology
London School of Hygiene & Tropical Medi

CAUSAL PROPHYLAXIS TEST NO: 1377 DATE: 7/12/82

COMPOUND: LON/ 1733 BOTTLE NO: BG66798 WR228708

FORMULATION: Tween 80/H_2O ROUTE: sc/~~ip/po~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
			(a)	(c)				
0	5/5	3/3	5.44	3.47				
			(b)	(d)				
3.0	3/3	3/3	4.81	3.52	NIL	NIL	NIL	INACTIVE
			(b)	(d)				
10.0	3/3	3/3	4.78	3.55	NIL	NIL	NIL	INACTIVE
			(b)	(d)				
30.0	1/3	3/3	> 10.81	3.49	> 5.37	NIL	> 5.37	ACTIVE
			(b)	(d)				
100.0	0/3	3/3	> 14	3.65	> 8.56	NIL	> 8.56	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ....30.0 - 100.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~MARKED~~ AT .....100.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W [illegible]
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 964 DATE: 8/7/82

COMPOUND: LON/ 1734 BOTTLE NO: BH89438 WR242511

FORMULATION: Tween 80/H_2O ROUTE: sc TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.12	(c) 3.27				
3.0	0/5	3/3	(b) > 14	(d) 3.31	> 8.88	NIL	> 8.88	FULLY ACTIVE
10.0	0/5	3/3	(b) > 14	(d) 3.54	> 8.88	NIL	> 8.88	FULLY ACTIVE
30.0	0/5	3/3	(b) > 14	(d) 3.74	> 8.88	NIL	> 8.88	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE < 3.0 .....mg/kg

RESIDUAL ACTIVITY: NIL

PRESENT AT ...30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 1377 DATE: 7/12/82

COMPOUND: LON/ 1736 BOTTLE NO: BJ78592 WR

FORMULATION: Tween 80/H_2O ROUTE: sc/~~XXXX~~ TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.44	(c) 3.47				
3.0	0/5	3/3	(b) > 14	(d) 3.62	> 8.56	NIL	> 8.56	FULLY ACTIVE
10.0	0/5	3/3	(b) > 14	(d) 3.52	> 8.56	NIL	> 8.56	FULLY ACTIVE
30.0	0/5	2/3	(b) > 14	(d) 3.57	> 8.56	NIL	> 8.56	FULLY ACTIVE ~ LD_{33}
90.0	0/5	1/3	(b) > 14	(d) 3.65	> 8.56	NIL	> 8.56	FULLY ACTIVE ~ LD_{66}
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE .....< 3.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~PROPHYLAXIS~~ AT ..100.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 964 DATE: 8/7/82

COMPOUND: LON/ 1716 BOTTLE NO: AJ63248 WR9792

FORMULATION: Tween 80/H_2O ROUTE: sc/[illegible] TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.12	(c) 3.27				
3.0	4/5	3/3	(b) > 9.07	(d) 3.19	> 3.95	NIL	> 3.95	ACTIVE
10.0	0/5	3/3	(b) > 14	(d) 3.26	> 8.88	NIL	> 8.88	FULLY ACTIVE
30.0	0/5	3/3	(b) > 14	(d) 3.37	> 8.88	NIL	> 8.88	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE .....3.0 - 10.0.....mg/kg

RESIDUAL ACTIVITY: NIL

[illegible] AT 30.0 .....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medici

CAUSAL PROPHYLAXIS TEST NO: 964

DATE: 8/7/82

COMPOUND: LON/ 1717

BOTTLE NO: AB65541 WR61112

FORMULATION: Tween 80/H_2O

ROUTE: sc/~~XXXX~~

TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice

PARASITE: P. yoelii nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	3/3	(a) 5.12	(c) 3.27				
3.0	5/5	3/3	(b) 5.10	(d) 3.30	NIL	NIL	NIL	INACTIVE
10.0	5/5	3/3	(b) 5.47	(d) 3.42	NIL	NIL	NIL	INACTIVE
30.0	5/5	3/3	(b) 5.05	(d) 3.17	NIL	NIL	NIL	INACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ..>30.0.....mg/kg

RESIDUAL ACTIVITY: NIL

~~XXXXXX~~ AT ..30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 1282 DATE:12/11/82

COMPOUND: LON/ 1718 BOTTLE NO: BD22997 WR158124

FORMULATION: Tween 80/H_2O ROUTE: sc/[illegible] TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: P. yoelii nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	4/4	3/3	(a) 5.87	(c) 3.82				
3.0	3/3	3/3	(b) 6.12	(d) 3.78	NIL	NIL	NIL	INACTIVE
10.0	2/3	3/3	(b) > 8.86	(d) 3.84	> 2.99	NIL	> 2.99	ACTIVE
30.0	0/3	3/3	(b) > 14	(d) 3.96	> 8.13	NIL	> 8.13	FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE ..10.0.-.30.0.....mg/kg

RESIDUAL ACTIVITY: NIL

[illegible] AT ...30.0.....mg/kg

MARKED AT .....mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETER
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF BLOOD SCHIZONTOCIDAL (4 DAY TEST) DATA.

LON or L I V No.	Suppliers No.	Route	N		NS		RC		P		B		PYR		ORA		N/1100	
			ED_{50}	ED_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}
1179	AW91877 WR159251	sc	9.0	265	100	0.4											200	0.75
		po	3.5	100	300	3.0											150	1.5
1528	FLOXACRINE	sc	0.9	1.9	3.1	1.6											0.9	0.5
1752	BKO2771 WR245082	sc	2.9	6.2	11.8	1.9											2.0	0.3
1753	BKO2780 WR246976	sc	7.0	39.0	15.0	0.4											20.5	0.3

ED_{50} / ED_{90} = mg/kg x 4 MTD = maximum tolerated dose

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER ..... LIV 1179 ..... PARASITE (SUB)SPECIES ..... P.berghei .....

FORMULATION ..... Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/~~IP/PO/IV~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X100
	1.0	5		-	77.8 ± 4.8
	3.0	5		-	66.2 ± 5.9
N	10.0	5	1	-	56.1 ± 3.7
	30.0	5		-	42.8 ± 3.7
	100.0	5		-	18.3 ± 3.8
	ø	10		18.0	
ED_{50}(range) 9.0(4.0-30)					
ED_{90}(range) 265 (120-850)†		†Interpolated graphically			
Resistance factor I_{90}					
	1.0	5		-	77.6 ± 7.4
	3.0	5		-	66.1 ± 5.2
NS	10.0	5	1	-	57.0 ± 3.1
	30.0	5		-	52.5 ± 4.4
	100.0	5		-	32.9 ± 7.4
	ø	10		16.1	
ED_{50}(range) 18.5 (7.5-60)					
ED_{90}(range) ≫ 100					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER ..... LIV 1179 ..... PARASITE (SUB)SPECIES ..... P.berghei

FORMULATION ..... Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/~~IRXRBXIX~~X

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X100
	1.0	5		-	100 ± 0.1
	3.0	5		-	82.0 ± 2.9
N/1100	10.0	5		-	73.8 ± 3.0
	30.0	5	1	-	70.0 ± 2.9
	100.0	5		-	41.8 ± 9.1
	Ø	10		12.0	

ED_{50}(range) 51 (10-100)

ED_{90}(range) 200 (35-400)

Resistance factor I_{90}

ED_{50}(range)

ED_{90}(range)

Resistance factor I_{90}

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TEST

(BLOOD SCHIZONTOCIDE)

COMPOUND NAME OR NUMBER LIV 1179 ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : ~~XXXX~~/PO/~~XX~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR x10
	1.0	5		-	60.7 ± 6.3
	3.0	5		-	48.1 ± 3.1
N	10.0	5	1	-	45.8 ± 3.5
	30.0	5*		-	36.1 ±
	100.0	5**		-	21.1 ±
	Ø	10		18.0	

ED_{50}(range) 3.5 (1.6-10)

ED_{90}(range) ⩾100

Resistance factor I_{90}

* 2/5 DIED

** 4/5 DIED

	1.0	5		-	77.0 ± 6.2
	3.0	5**		-	77.0 ±
NS	10.0	5*	1	-	73.0 ± 3.3
	30.0	5*		-	60.4 ± 1.4
	100.0	5**		-	24.2 ±
	Ø	10		16.1	

ED_{50}(range) 25 (11-45)

ED_{90}(range) 300 (125-640)†

Resistance factor I_{90}

* 1/5 DIED

** 4/5 DIED

† INTERPOLATED GRAPHICALLY

Date: 18/1/83

Principal Investigator: Professor W.Peters

Department of Medical Protozoology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TEST [illegible]

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER LIV 1179 ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	1.0	5		-	100 ±
	3.0	5		-	100 ±
N/1100	10.0	5	1	-	100 ±
	30.0	5		-	100 ± 6.5
	100.0	5		-	53.2 ± 10.6
	Ø	10		12.0	

ED_{50}(range) 98 (49-115)

ED_{90}(range) 150 (75-180)

Resistance factor I_{90}

ED_{50}(range)

ED_{90}(range)

Resistance factor I_{90}

Date: 18/1/83

Principal Investigator: Professor W.Peters

Department of Medical Protozoology

[illegible] of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME LIV 1528

OR NUMBER FLOXACRINE PARASITE (SUB)SPECIES P.berghei

FORMULATION Tween 80 / H_2O ROUTE OF ADMINISTRATION : SC/~~IP/PO/IV~~

MAXIMUM TOLERATED DOSE (MTD) > 30 MG/KG X 4.

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X100
	1.0	5		-	61.4 ± 3.7
	3.0	5		-	0.9 ± 0.6
N	10.0	5	1	-	0
	30.0	5		-	0
	Ø	10		16.2	

ED_{50}(range) 0.9(0.5-1.3)

ED_{90}(range) 1.9(1.2-2.7)

Resistance factor f_{90} 1.0

	0.3	5		-	60.5 ± 8.4
	1.0	5		-	50.0 ± 3.5
NS	3.0	5	1	-	11.0 ± 3.6
	10.0	5		-	1.1 ± 0.5
	Ø	10		20.0	

ED_{50}(range) 0.6(0.3-1.1)

ED_{90}(range) 3.1(1.7-6.0)

Resistance factor f_{90} 1.6

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDE)

COMPOUND NAME LIV 15.28

OR NUMBER ..... FLOXACRINE ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION ..... Tween 80 / H_2O ... ROUTE OF ADMINISTRATION : SC/~~IP/PO/IV~~

MAXIMUM TOLERATED DOSE (MTD) ..30... MG/KG X ..4..

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X100
	0.1	5		-	94.8 ± 4.4
	0.3	5		-	71.7 ± 4.1
N/1100	1.0	5	1	-	10.5 ± 3.1
	3.0	5		-	0.3 ± 0.2
	Ø	10		19.1	

ED_{50}(range)	0.33(0.26-0.64)
ED_{90}(range)	0.9(0.7-1.8)
Resistance factor I_{90}	0.5

ED_{50}(range)	
ED_{90}(range)	
Resistance factor I_{90}	

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME BRO.2771
WR.245082

OR NUMBER ION 1752 ..... PARASITE (SUB)SPECIES P.berghei

FORMULATION Tween 80 / H_2O ... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >30 ... MG/KG X 4 .

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PP / Control PP X100
	1.0	5		-	73.5 ± [illegible]
	3.0	5		-	40.1 ± [illegible]
N	10.0	5	1	-	23.5 ± [illegible]
	30.0	5		-	0
	Ø	10		16.2	

ED_{50}(range) 2.9(1.3-7.2)

ED_{90}(range) 6.2(2.9-15.6)

Resistance factor I_{90} 1.0

	1.0	5		-	[illegible] ± [illegible]
	3.0	5		-	[illegible] ± [illegible]
NS	10.0	5	1	-	[illegible] ± [illegible]
	30.0	5		-	[illegible] ± [illegible]
	Ø	10		20.0	

ED_{50}(range) 1.4(0.8-2.5)

ED_{90}(range) 11.8(6.8-21.0)

Resistance factor I_{90} 1.9

Date: 18/1/83

Principal Investigator: Professor A. Peters
Department of Medical Protozoology
[illegible] School of Hygiene & Tropical Medicine

COMPOUND NAME [illegible]

OR NUMBER [illegible] PARASITE (SUB)SPECIES [illegible]

FORMULATION [illegible] ROUTE OF ADMINISTRATION : SC/[illegible]

MAXIMUM TOLERATED DOSE (MTD) [illegible] MG/KG X [illegible]

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR x 100
	1.0	5		-	60.7 ± [illegible]
	3.0	5		-	1.4 ± 0.7
N/1100	10.0	5	1	-	[illegible]
	30.0	5		-	0
	Ø	10		19.1	

ED_{50}(range) 1.2(1.0-1.3)

ED_{90}(range) 2.0(1.7-2.5)

Resistance factor I_{90} 0.3

ED_{50}(range)

ED_{90}(range)

Resistance factor I_{90}

Date: 18/1/83

Principal Investigator: Professor [illegible]

Department of Medical Protozoology

[illegible] School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME BRO2780 WR246976

OR NUMBER ION 1753 ..... PARASITE (SUB)SPECIES P.berghei

FORMULATION ..Tween 80 / H_2O... ROUTE OF ADMINISTRATION : SC/~~IP/PO/IV~~

MAXIMUM TOLERATED DOSE (MTD) >100 ..... MG/KG X 4 ...

Strain	Daily dose mg/kg DO-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X100
	1.0	5		-	85.8 ± 2.8
	3.0	5		-	69.1 ± 3.3
N	10.0	5	1	-	52.5 ± 8.7
	30.0	5		-	33.3 ± 7.6
	100.0	5		-	2.5 ± 0.9
	Ø	10		16.2	
ED_{50}(range) 7.0(3.5-20)					
ED_{90}(range) 39.0(19-110)					
Resistance factor I_{90} 1.0					
	1.0	5		-	75.0 ± 4.1
	3.0	5		-	59.0 ± 5.2
NS	10.0	5	1	-	46.0 ± 10.2
	30.0	5		-	8.5 ± 1.1
	100.0	5		-	0.05 ± 0.05
	Ø	10		20.0	
ED_{50}(range) 5.0(1.8-9.0)					
ED_{90}(range) 15.0(5.2-43.0)					
Resistance factor I_{90} **0.4**					

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER: BF0?780 / WR2?6?? / LON ??   PARASITE (SUB)SPECIES: P.berghei

FORMULATION: Tween 80 / H_2O ROUTE OF ADMINISTRATION : SC

MAXIMUM TOLERATED DOSE (MTD) >100 MG/KG X 4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR × 100
	0.3	5		-	73.[illegible] ± [illegible]
	1.0	5		-	69.1 ± 1.[illegible]
N/1100	3.0	5	1	-	55.0 ± [illegible]
	10.0	5		-	41.[illegible] ± [illegible]
	30.0	5			[illegible] ± [illegible]
	∅	10		19.1	

ED_{50}(range) 2.9(0.6-8.8)

ED_{90}(range) 20.5(4.6-58.0)

Resistance factor I_{90} 0.5

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR × 100

ED_{50}(range)

ED_{90}(range)

Resistance factor I_{90}

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
[illegible] Hygiene & Tropical Medicine

BLOOD SCHIZONTOCIDAL ACTIVITY

SINGLE DOSE ED_{90} TESTS

STRAIN	MEFLOQUINE		PYRIMETHAMINE (P)		SULFADOXINE (S)		P:S (1:3)	
	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}
N	15.3	1.0	2.0	1.0	10.1	1.0	0.5	1.0
N/1100	1000	>65	13.8	6.9	4.2	0.4	1.3	2.6
PFM/37	250	16.3	10.3	5.2	1.3	1.3	0.9	1.8
NS	10.0	0.7	2.0	1.0	1.5	0.15	0.2	0.4
NS/1100	1000	65	2.2	1.1	1.7	0.17	0.52	1.0
MPS/28	66.0	4.3	2.1	1.1	1.7	0.17	0.32	0.64
FY/65/1	13.0	0.85	130	65.0	290	28.7	88.0	176
MFY/30	170	11.1	49.0	24.5	195	19.3	100	200

SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 34

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER ..... Mefloquine ..... PARASITE (SUB)SPECIES ..... P.berghei .....

FORMULATION ..... Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/~~MXXPOXXMX~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Singledose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	3.0	5		-	58.9 ± 6.5
	10.0	5		-	37.9 ± 7.3
N	30.0	5	1	-	1.1 ± 0.6
	100.0	5		-	0
	Ø	10		19.4	
ED_{50}(range)5.9 (3.0-9.0)					
ED_{90}(range)15.3(7.0-24.0)					
Resistance factor I_{90} 1.0					
	3.0	5		-	70.8 ± 5.0
	10.0	5		-	14.1 ± 9.5
NS	30.0	5	1	-	0.07 ± 0.07
	100.0	5		-	0
	Ø	10		29.2	
ED_{50}(range) 4.4(3.4-6.0)					
ED_{90}(range)10.0(7.8-14.0)					
Resistance factor I_{90} 0.7					

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 35

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER Pyrimethamine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : ~~SC~~/IP/~~PO~~/~~IM~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	0.3	5		-	56.5 ± 3.2
	1.0	5		-	26.1 ± 5.5
N	3.0	5	1	-	21.6 ± 2.1
	10.0	5		-	0.4 ± 0.3
	30.0	5		-	0
	Ø	10		19.4	
ED_{50}(range)0.5 (0.2-1.4)					
ED_{90}(range)2.0 (1.0-5.4)					
Resistance factor I_{90} 1.0					
	0.3	5		-	49.3 ± 13.2
	1.0	5		-	32.7 ± 5.4
NS	3.0	5	1	-	25.9 ± 9.4
	10.0	5		-	0.07 ± 0.07
	30.0	5		-	0
	Ø	10		29.2	
ED_{50}(range) 0.5 (0.2-2.5)					
ED_{90}(range) 2.0 (1.0-11.0)					
Resistance factor I_{90} 1.0					

Date: 18/1/83

Principal Investigator: Professor W.Peters
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London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER ..... Sulphadoxine ..... PARASITE (SUB)SPECIES ..... P.berghei .....

FORMULATION ..... Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/IP/~~XXXXX~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO...	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	0.3	5		-	87.0 ± 5.3
	1.0	5		-	50.1 ± 3.7
N	3.0	5	1	-	40.0 ± 2.7
	10.0	5		-	25.8 ± 3.4
	Ø	10		19.4	

ED_{50}(range) 1.7 (0.9-4.6)

ED_{90}(range) 10.1 (5.5-2.9)

Resistance factor I_{90} 1.0

	0.3	5		-	47.9 ± 7.7
	1.0	5		-	25.3 ± 8.2
NS	3.0	5	1	-	5.0 ± 3.2
	10.0	5		-	0.07 ± 0.07
	Ø	10		29.2	

ED_{50}(range) 0.4 (0.2-0.7)

ED_{90}(range) 1.5 (0.9-2.7)

Resistance factor I_{90} 0.15

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY : ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME 1:3
OR NUMBER Pyrimethamine/Sulphadoxine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/IP/[illegible]

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	0.04	5		-	62.4 ± 7.5
	0.13	5		-	44.0 ± 3.8
N	0.4	5	1	-	31.6 ± 1.6
	1.3	5		-	8.2 ± 1.9
	4.0	5		-	0.1 ± 0.1
	Ø	10		19.4	
ED_{50}(range) 0.11(0.05-0.29)					
ED_{90}(range) 0.5 (0.2-1.3)					
Resistance factor I_{90} 1.0					
	0.04	5		-	47.9 ± 7.7
	0.13	5		-	25.3 ± 8.2
NS	0.4	5	1	-	5.0 ± 3.2
	1.3	5		-	0.07 ± 0.07
	4.0	5		-	0
	Ø	10		29.2	
ED_{50}(range) 0.05(0.03-0.08)					
ED_{90}(range) 0.2 (0.1-0.3)					
Resistance factor I_{90} 0.4					

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

COMPOUND NAME OR NUMBER Mefloquine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC XXXXXXXXXX

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR x10
	3.0	5		-	75.7 ± 14.9
	10.0	5		-	35.5 ± 11.3
MPS	30.0	5	1	-	26.2 ± 8.6
	100.0	5		-	9.3 ± 5.4
	Ø	10		10.7	

ED_{50}(range) 9.5 (3.5-17.5)

ED_{90}(range) 66.0 (25-120)

Resistance factor I_{90}

	3.0	5		-	82.4 ± 2.2
	10.0	5		-	74.4 ± 12.6
NC/1100	30.0	5	1	-	54.2 ± 1.4
	100.0	5		-	44.5 ± 2.5
	Ø	5		12.5	

ED_{50}(range) 52 (22-245)

ED_{90}(range) > 1000

Resistance factor I_{90}

Date: 18/1/83

Principal Investigator: Professor W.Peters
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London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER Pyrimethamine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/IP~~XPOXXX~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	0.3	5		-	85.2 ± 6.8
	1.0	5		-	72.9 ± 11.8
MPS	3.0	5	1	-	5.6 ± 2.7
	10.0	5		-	0.02 ± 0.02
	30.0	5		-	0
	∅	10		10.7	
ED_{50}(range) 0.8 (0.5-1.8)					
ED_{90}(range) 2.1 (1.4-4.4)					
Resistance factor I_{90}					
	0.1	5		-	81.4 ± 6.6
	0.3	5		-	52.3 ± 12.4
NS/1100	1.0	5	1	-	30.1 ± 11.8
	3.0	5		-	17.8 ± 5.2
	10.0	5		-	1.0 ± 0.5
	∅	5		12.5	
ED_{50}(range) 0.4 (0.2-1.1)					
ED_{90}(range) 2.2 (1.2-6.5)					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS (BLOOD SCHIZONTOCIDES)

TABLE 40

COMPOUND NAME OR NUMBER Sulfadoxine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : XSC/IP/APOXXXX

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	0.3	5		-	80.4 ± 4.8
	1.0	5		-	40.6 ± 5.2
MPS	3.0	5	1	-	2.4 ± 1.4
	10.0	5		-	0
	Ø	10		10.7	
ED_{50}(range) 0.6 (0.5-0.9)					
ED_{90}(range) 1.7 (1.2-2.4)					
Resistance factor I_{90}					
	0.3	5		-	80.6 ± 2.2
	1.0	5		-	24.0 ± 5.1
NS/1100	3.0	5	1	-	9.6 ± 3.7
	10.0	5		-	0.5 ± 0.3
	30.0	5		-	0
	Ø	5		12.5	
ED_{50}(range) 0.6 (0.4-1.0)					
ED_{90}(range) 1.7 (1.2-2.7)					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 41

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER Pyrimethamine:Sulfadoxine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : ~~XSC~~/IP/~~XPOXIVX~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DC	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	0.075	5		-	75.7 ± 15.6
	0.15	5		-	63.6 ± 18.5
MPS	0.31	5		-	8.8 ± 5.4
	0.62	5	1	-	2.1 ± 1.4
	1.25	5		-	0.05 ± 0.04
	2.5	5		-	0
	Ø	10		10.7	
ED_{50}(range) 0.13 (0.09-0.27)					
ED_{90}(range) 0.32 (0.21-0.66)					
Resistance factor I_{90}					
	0.075	5		-	73.8 ± 7.1
	0.15	5		-	59.5 ± 6.9
NS/1100	0.31	5		-	14.4 ± 3.9
	0.62	5	1	-	4.2 ± 1.2
	1.25	5		-	2.0 ± 1.8
	2.5	5		-	0.2 ± 0.2
	Ø	5		12.5	
ED_{50}(range) 0.14 (0.09-0.23)					
ED_{90}(range) 0.52 (0.32-0.78)					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

P.berghei

PARASITE (SUB)SPECIES .....

ROUTE OF ADMINISTRATION : XSS/IP/XXXXX

..... MG/KG X ...

Drug	Single dose mg/kg b.w.	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X100
	0.3	5		-	100 ± 11.6
	1.0	5		-	83.2 ± 7.1
PFMA	3.0	5	1	-	32.3 ± 5.2
	10.0	5		-	17.0 ± 6.9
	30.0	5		-	2.6 ± 1.5
	Ø	10		11.4	
ED_{50} (range) 3.5 (1.6-7.0)					
ED_{90} (range) 10.3 (4.7-20.5)					
Resistance factor I_{90}					
	0.1	5		-	76.9 ± 7.2
	0.3	5		-	54.5 ± 3.9
N/1100	1.0	5	1	-	45.7 ± 12.2
	3.0	5		-	29.4 ± 5.6
	Ø	10		13.4	
ED_{50} (range) 0.6 (0.3-1.5)					
ED_{90} (range) 13.8 (6.8-34)					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
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SUMMARY ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER: Pyrimethamine/Sulphadoxine

PARASITE (SUB)SPECIES: P.berghei

FORMULATION: 1:3 in Tween $80/H_2O$

ROUTE OF ADMINISTRATION : ~~SC~~/IP/~~PO/IV~~

MAXIMUM TOLERATED DOSE (MTD) .... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X100
	0.15	5		-	68.8 ± 13.1
	0.31	5		-	32.1 ± 10.7
PFMA	0.62	5		-	20.0 ± 6.1
	1.25	5		-	11.4 ± 5.0
	2.5	5	1	-	5.2 ± 0.9
	5.0	5		-	0.4 ± 0.3
	10.0	5		-	0
	20.0	5		-	0
	Ø	10		11.1	
ED_{50}(range) 0.26 (0.18-0.68)					
ED_{90}(range) 0.88 (0.48-1.9)					
Resistance factor I_{90}					
	0.075	5		-	100 ± 4.2
	0.15	5		-	83.3 ± 5.0
N/1100	0.31	5		-	77.1 ± 9.0
	0.62	5	1	-	19.2 ± 7.6
	1.25	5		-	10.4 ± 5.0
	2.5	5		-	7.1 ± 1.6
	Ø	10		9.6	
ED_{50}(range) 0.28 (0.2-0.76)					
ED_{90}(range) 1.3 (0.7-2.6)					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME Mefloquine

OR NUMBER ... . PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/[redacted]

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR x10
	3.0	5		-	81.8 ± 11.9
	10.0	5		-	62.3 ± 12.3
PFMA	30.0	5	1	-	54.6 ± 5.5
	100.0	5		-	27.2 ± 9.7
	Ø	10		11.1	
ED_{50}(range)25.0(8.0-52)					
ED_{90}(range)250 (80-520)		(= >MTD) Graphically interpolated			
Resistance factor I_{90}					
	3.0	5		-	91.5 ± 3.2
	10.0	5		-	84.8 ± 5.0
N/1100	30.0	5	1	-	62.1 ± 4.2
	100.0	5		-	50.6 ± 15.8
	Ø	10		9.6	
ED_{50}(range)95 (48-215)					
ED_{90}(range) >1000 (= >MTD)		Graphically interpolated			
Resistance factor I_{90}					

Date: 18/1/83

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SUMMARY OF ANTIMALARIAL DRUG TESTS

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER ..... Mefloquine ..... PARASITE (SUB)SPECIES ..... P.berghei

FORMULATION ..... Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/[illegible]

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR x10
	3.0	5		-	88.1 ± 5.8
	10.0	5		-	6.6 ± 1.6
FY/65	30.0	5	1	-	2.0 ± 1.5
	100.0	5		-	0
	Ø	10		13.0	
ED_{50}(range) 5.0 (3.0-8.0)					
ED_{90}(range) 13.0 (7,5-23)					
Resistance factor I_{90}					
	3.0	5		-	89.1 ± 5.6
	10.0	5		-	71.9 ± 10.5
MFY	30.0	5	1	-	36.2 ± 7.0
	100.0	5		-	20.4 ± 6.6
	Ø	10		9.9	
ED_{50}(range) 21 (12-35)					
ED_{90}(range) 170 (100-280)					
Resistance factor I_{90}					

(= >MTD) Graphically interpolated

Date: 18/1/83

Principal Investigator: Professor W.Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE
(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER Pyrimethamine/Sulphadoxine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION 1:3 in Tween 80/H_2O ROUTE OF ADMINISTRATION : ~~XXX~~/IP/~~XXXXX~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	2.5	5		-	74.8 ± 6.8
	5.0	5		-	65.4 ± 11.8
FY/65	10.0	5	1	-	49.5 ± 6.2
	20.0	5		-	33.8 ± 1.6
	40.0	5		-	26.5 ± 4.0
	Ø	10		13.0	
ED_{50}(range) 9.5 (5.5-17.0)					
ED_{90}(range) 88 (52-155)					
Resistance factor I_{90}					
	2.5	5		-	100 ± 3.1
	5.0	5		-	79.4 ± 6.4
MFY	10.0	5	1	-	68.7 ± 8.5
	20.0	5		-	30.3 ± 5.8
	40.0	5		-	26.9 ± 1.9
	Ø	10		9.9	
ED_{50}(range) 15 (7.0-30)					
ED_{90}(range) 100 (50-210)					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 47

BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER Pyrimethamine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	1.0	5		-	69.2 ± 8.1
	3.0	5		-	50.9 ± 10.0
FY/65	10.0	5	1	-	41.5 ± 1.5
	30.0	5		-	31.5 ± 4.4
	60.0	5		-	16.2
	Ø	10		13.0	
ED_{50}(range) 4.8 (7.0-12.0)					
ED_{90}(range) 130 (45 - 300)					
Resistance factor I_{90}					
	1.0	5		-	70.2 ± 2.4
	3.0	5		-	30.7 ± 9.8
MFY	10.0	5	1	-	21.6 ± 5.0
	30.0	5		-	19.9 ± 9.7
	60.0	5		-	8.9 ± 4.8
	Ø	10		8.8	
ED_{50}(range) 3.0 (<1 - 9.5)					
ED_{90}(range) 49 (7.5 - 160)					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 48

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME OR NUMBER Sulphadoxine ..... PARASITE (SUB)SPECIES P.berghei .....

FORMULATION Tween 80/H_2O ..... ROUTE OF ADMINISTRATION : ~~XSC~~/IP/~~XPO~~/~~XIV~~

MAXIMUM TOLERATED DOSE (MTD) ..... MG/KG X ...

Strain	Single dose mg/kg DO	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR / Control PR X10
	3.0	5		-	61.2 ± 2.8
	10.0	5		-	51.5 ± 1.5
FY/65	30.0	5	1	-	34.6 ± 2.5
	100.0	5		-	17.4 ± 4.9
	Ø	10		13.0	
ED_{50}(range) 8.0 (3.8 - 12.5)					
ED_{90}(range) 290 (140 - 430)					
Resistance factor I_{90}					
	3.0	5		-	80.9 ± 9.4
	10.0	5		-	71.4 ± 8.7
MFY	30.0	5	1	-	42.5 ± 15.5
	100.0	5		-	17.7 ± 7.0
	Ø	10		8.8	
ED_{50}(range) 17.0 (8.2 - 43)					
ED_{90}(range) 195 (90 - 470)					
Resistance factor I_{90}					

Date: 18/1/83

Principal Investigator: Professor W.Peters
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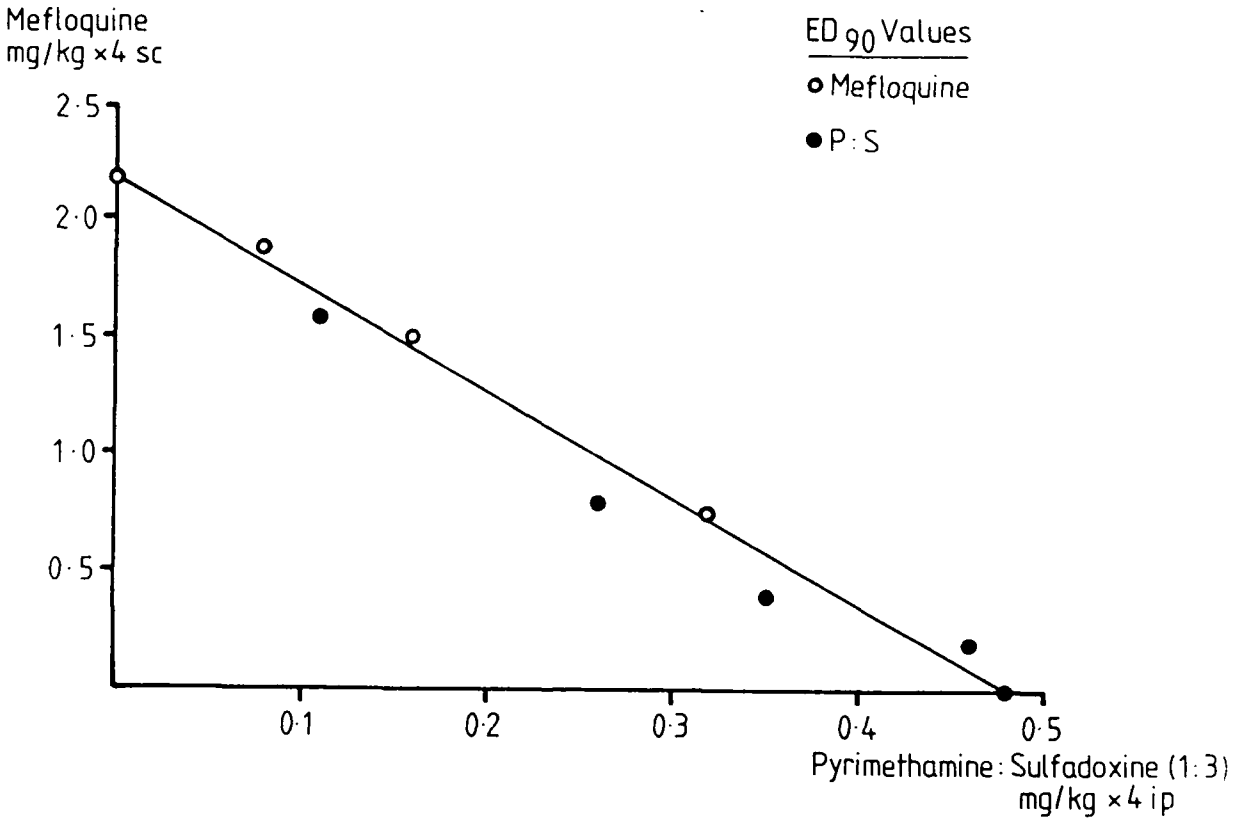
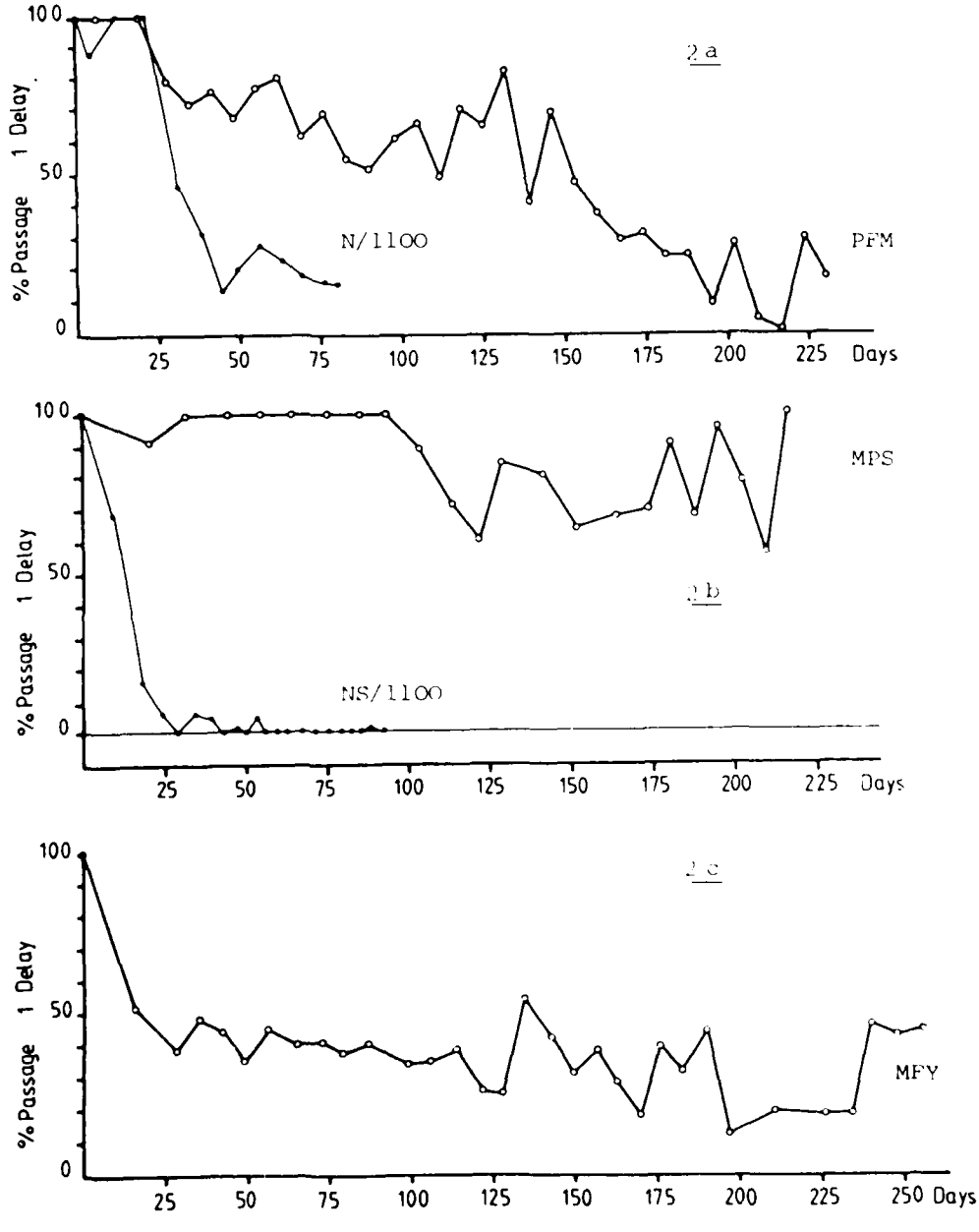


Figure 1. The interaction of mefloquine with a 1:3 pyrimethamine-sulfadoxine mixture in different proportions to show the ED_{90} of mefloquine(M) with different levels of PS, or PS with different levels of M against P.berghei N in the "4-day test". An additive effect is shown when all points fall near the line joining the ED_{90} levels for each compound (i.e. M or PS) used alone, as in this experiment.

Figure 2. Changing trends of the "2 delay time" with successive passages under drug pressure as a function of the time the lines were maintained. Individual points indicate the "2 delay times" of parasites in individual passages, expressed as a percentage of the "2 delay time" of the initial passage.



2 a. P.berghei N exposed to mefloquine alone (N/1100) or a 300:1:3 mixture of mefloquine (M), pyrimethamine (P) and sulfadoxine (S) (PFM line)

2 b. "P.berghei NS" exposed to M (NS/1100 line) or MPS (MPS line) in the same ratios.

2 c. P.berghei NK65 FY exposed to M and PS in a 1:1:3 ratio (MFY line)

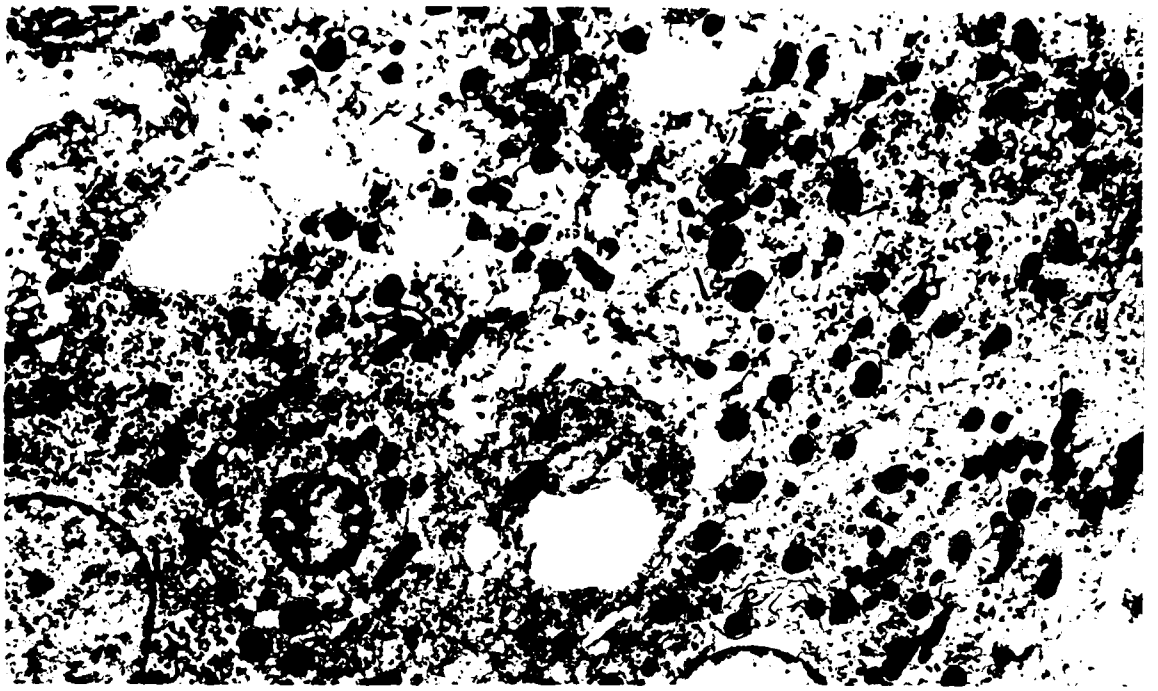


Figure 3 Controls x 5200
These show uninfected liver sections exposed to 3 mg/kg WR225,448 The liver cells are vacuolated and disrupted. There are considerable lipid deposits and many of the mitochondria are affected. In general this liver looks pretty toxic.

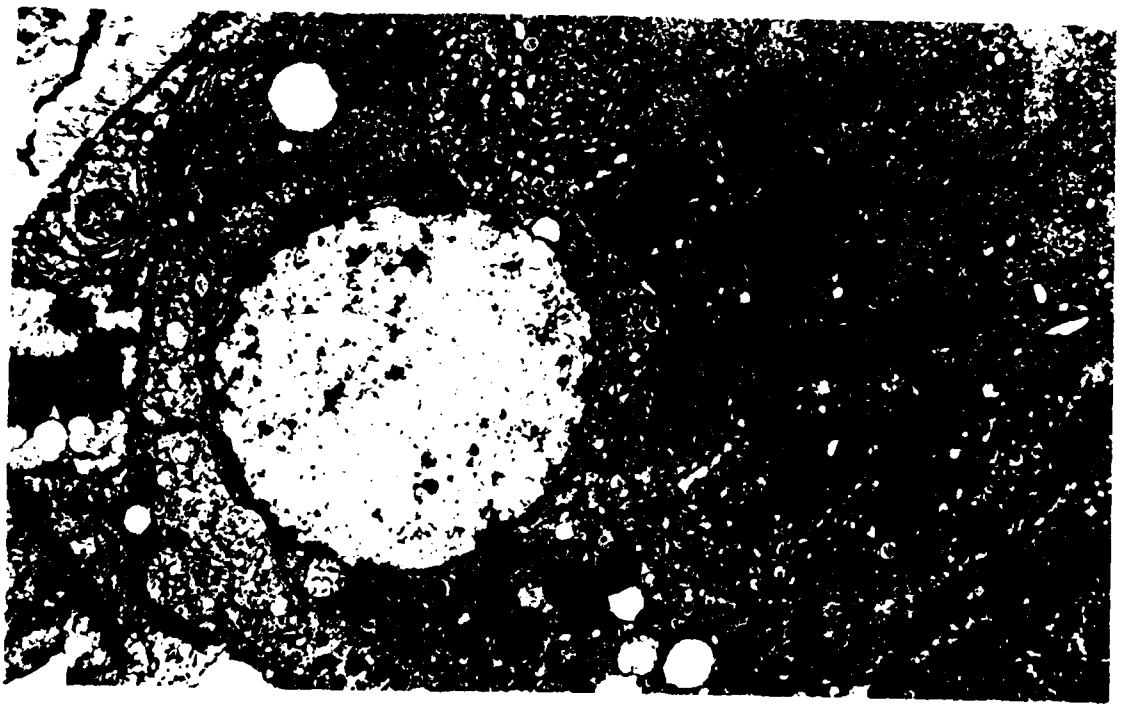


Figure 4 Low power x 6600
Infected liver sections treated 1 mg/kg WR 225,448. Schizont shows normal peripheral enzyme production, but no liberation of enzyme granules.Adjacent hepatocyte tissue is apparently unaffected at schizont/hepatocyte interface.

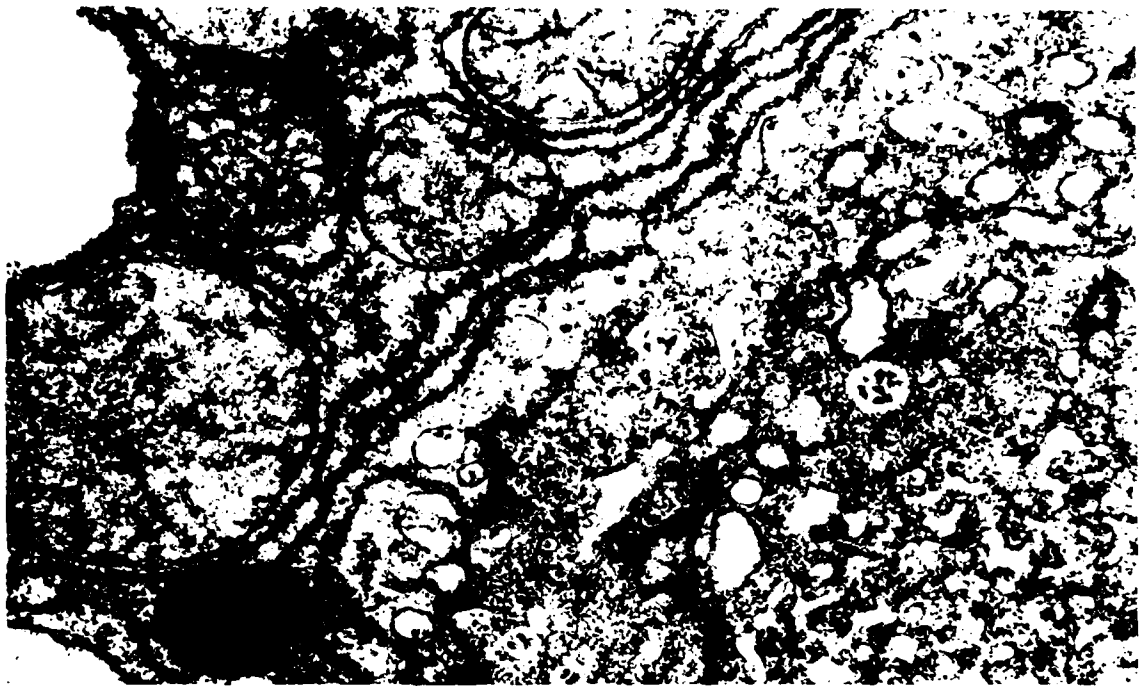
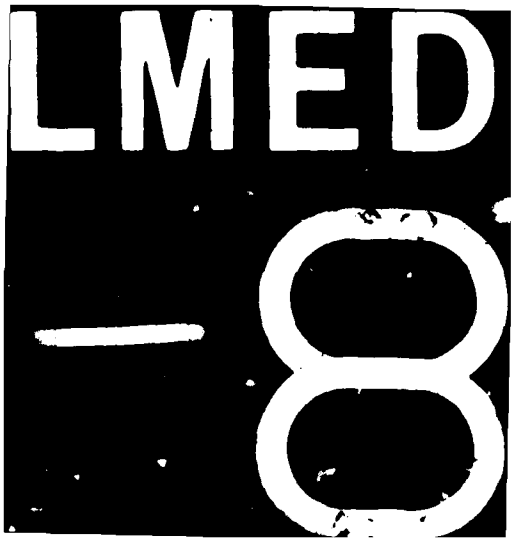


Figure 5 High power x 26000
Same material as above, showing enzyme granule vacuoles intact at schizont boundary, and adjacent host cell mitochondria unaffected. Note extensive enzyme granule production and swollen mitochondria.
In addition many of the nuclei in the schizonts show marked separation and blebbing of their surrounding membranes.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